IN THE SPECIFICATION:

Please replace the paragraph on page 1, lines 3-4, with the following amended paragraph:

This filing is a divisional of commonly assigned, co-pending application Ser. No. 09/853,180, filed May 10, 2001, which claims benefit of U.S. Provisional Patent Application no. 60/203,426, filed May 10, 2000, each of which is incorporated herein by reference in its entirety.

Please replace the paragraph on page 3, lines 5-20, with the following amended paragraph:

The present invention provides a substantially pure or recombinant polypeptide comprising at least ten contiguous amino acids of the intracellular portion of SEQ ID NO: 2. In certain embodiments, the polypeptide: comprises at least 25 contiguous amino acids of the intracellular portion of SEQ ID NO: 2; is recombinant, comprising the intracellular portion of SEQ ID NO: 2; further comprises at least ten contiguous amino acids of the non-intracellular portion of SEQ ID NO: 2; comprises at least 25 amino acids of the extracellular portion of SEQ ID NO: 2; comprises the mature SEQ ID NO: 2; or is a substantially pure natural polypeptide. In others, the recombinant polypeptide: consists of the mature sequence of ~~Table 1~~ SEQ ID NO:2; is an unglycosylated polypeptide; is from a human; comprises at least 40 contiguous amino acids of SEQ ID NO: 2; exhibits at least three nonoverlapping segments of at least fifteen contiguous amino acids of SEQ ID NO: 2; is a natural polymorphic variant of SEQ ID NO: 2; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate DCRS5; has a molecular weight of at least 30 kD with natural glycosylation; is a synthetic polypeptide; is in a sterile form; is in an aqueous or buffered solution; is attached to a solid substrate; is conjugated to another chemical moiety; or is physically associated with an IL-12Rβ1 polypeptide.

Please replace the paragraph beginning on page 3, line 21, and continuing to page 4, line 12, with the following amended paragraph:

Other embodiments of the invention provide: a substantially pure or recombinant polypeptide comprising at least two distinct nonoverlapping segments of at least six contiguous amino acids of the intracellular portion of SEQ ID NO:2; a substantially pure or recombinant polypeptide comprising at least twelve contiguous amino acids of the intracellular portion of SEQ ID NO: 2; or a substantially pure natural sequence polypeptide comprising mature SEQ ID NO: 2. In particular forms, the polypeptide comprising at least two distinct nonoverlapping segments of at least six contiguous amino acids of the intracellular portion of SEQ ID NO: 2 will be where: the distinct nonoverlapping segments: include one of at least twelve amino acids; include one of at least seven amino acids and a second of at least nine amino acids; include a third distinct segment of at least six amino acids; or comprise one of R355-L373, P378-L405, V407-D426, K428-D439, P441-V452, I454-G460, I465-T587, or N592-606; or the polypeptide further comprises at least two distinct nonoverlapping segments of at least six contiguous amino acids of the extracellular portion of SEQ ID NO: 2. Alternatively, the polypeptide comprising at least twelve contiguous amino acids of the intracellular portion of SEQ ID NO: 2 will be one where: the at least twelve contiguous amino acid segment comprises one of R355-L373, P378-L405, V407-D426, K428-D439, P441-V452, I454-G460, I465-T587, or N592-606; or the polypeptide further comprises at least two distinct nonoverlapping segments of at least six contiguous amino acids of the extracellular portion of SEQ ID NO: 2. Or, the pure natural sequence polypeptide comprising mature SEQ ID NO: 2 may further comprising a purification or detection epitope. Such polypeptides may: consist of the mature sequence of ~~Table 1~~ SEQ ID NO:2; be an unglycosylated polypeptide; be from a human; comprise at least 40 contiguous amino acids of SEQ ID NO: 2; exhibit at least three nonoverlapping segments of at least fifteen contiguous amino acids of SEQ ID NO: 2; be a natural polymorphic variant of SEQ ID NO: 2; have a length at least about 30 amino acids; exhibit at least two non-overlapping epitopes which are specific for a primate DCRS5 (SEQ ID NO:2); have a molecular weight of at least 30 kD with natural glycosylation; be a synthetic polypeptide; be in a ~~steril~~ sterile form; be in an aqueous or buffered solution;

be attached to a solid substrate; be conjugated to another chemical moiety; or be physically associated with an IL-12Rβ1 polypeptide.

Please replace the paragraph on page 5, lines 11-21, with the following amended paragraph:

The invention also provides an isolated or recombinant nucleic acid encoding the DCRS5 (SEQ ID NO:2) polypeptide, wherein the: DCRS5 is from a human; or the nucleic acid: encodes an antigenic peptide sequence of ~~Table 1~~ SEQ ID NO:2; encodes a plurality of antigenic peptide sequences of ~~Table 1~~ SEQ ID NO:2; exhibits identity over at least thirteen nucleotides to a natural cDNA encoding the segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a primate; comprises a natural full length coding sequence; is a hybridization probe for a gene encoding the DCRS5 (SEQ ID NO:2); or is a PCR primer, PCR product, or mutagenesis primer. Cells comprising the recombinant nucleic acid are provided, including where the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell.

Please delete the paragraph on page 8, line 7.

Please delete the paragraph on page 9, lines 1-54.

Please delete the paragraph on page 10, lines 1-55.

Please delete the paragraph on page 11, lines 1-55.

Please delete the paragraph on page 12, lines 1-43.

Please delete the paragraph on page 13, lines 1-28.

Please replace the paragraph on page 13, lines 31-33, with the following rewritten paragraph:

~~Table 3~~ Table 1: Alignment of various cytokine receptor subunits. Human DCRS5 is SEQ ID NO:2. Human IL-6 receptor protein gp130 is ~~SEQ ID NO: 4~~ SEQ ID NO:3 (GenBank M57230); human IL-12 receptor beta2 subunit is ~~SEQ ID NO: 5~~ SEQ ID NO:4 (GenBank U64198).

Please replace the paragraph on page 15, lines 22-26, with the following rewritten paragraph:

~~Table 3~~ Table 1 shows comparison of the available sequences of primate receptor subunits with the primate, e.g., human DCRS5 (IL-30R). The DCRS5 shows similarity to the IL-6 receptor subunit gp130 (e.g., IL-6R subunit) and the IL-12Rβ2 subunit. The DCRS5 exhibits structural features of a beta subunit, but the actual sequence of protein interactions and signaling remains unresolved.

Please replace the paragraph on page 15, lines 27-41, with the following rewritten paragraph:

-- As used herein, the term DCRS5 shall be used to describe a protein comprising the amino acid sequence shown in ~~Table 1~~ SEQ ID NO:2. In many cases, a substantial fragment thereof will be functionally or structurally equivalent, including, e.g., additional extracellular segments. The invention also includes a protein variation of the respective DCRS5 allele whose sequence is provided, e.g., a mutein or other construct. Typically, such variants will exhibit less than about 10% sequence differences with the target region, and thus will often have between 1- and 11-fold substitutions, e.g., 2-, 3-, 5 , 7-fold, and others. It also encompasses allelic and other variants, e.g., natural polymorphisms, of the protein described. Typically, it will bind to its corresponding biological ligand, perhaps in a dimerized state with an alpha receptor subunit, with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. The term shall also

be used herein to refer to related naturally occurring forms, e.g., alleles, polymorphic variants, and metabolic variants of the mammalian protein. Preferred forms of the receptor complexes will bind the appropriate ligand with an affinity and selectivity appropriate for a ligand-receptor interaction.

Please replace the paragraph on page 16, lines 1-4, with the following rewritten paragraph:

This invention also encompasses combinations of proteins or peptides having substantial amino acid sequence identity with the amino acid sequence ~~in Table 1~~ SEQ ID NO:2. It will include sequence variants with relatively few substitutions, e.g., preferably fewer than about 3-5.

Please replace the paragraph on page 16, lines 15-35, with the following rewritten paragraph:

Amino acid sequence homology, or sequence identity, is determined by optimizing residue matches. In some comparisons, gaps may be introduces, as required. See, e.g., Needleham, et al., (1970) J. Mol. Biol. 48:443-453; Sankoff, et al., (1983) chapter one in Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group (GCG), Madison, WI; each of which is incorporated herein by reference. This changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences are intended to include natural allelic and interspecies variations in the cytokine sequence. Typical homologous proteins or peptides will have from 50 100% homology (if gaps can be introduced), to 60 100% homology (if conservative substitutions are included) with an amino acid sequence segment of ~~Table 1~~ SEQ ID NO:2. Homology measures will be at least about 70%, generally at least 76%, more generally at least 81%, often at least 85%, more often at least 88%, typically at least

90%, more typically at least 92%, usually at least 94%, more usually at least 95%, preferably at least 96%, and more preferably at least 97%, and in particularly preferred embodiments, at least 98% or more. The degree of homology will vary with the length of the compared segments. Homologous proteins or peptides, such as the allelic variants, will share most biological activities with ~~the embodiments described in Table 1~~ SEQ ID NO:2, particularly the intracellular portion.

Please replace the paragraph on page 18, lines 4-9, with the following rewritten paragraph:

The DCRS5 (SEQ ID NOs:1 or 2) has the characteristic motifs of a receptor signaling through the JAK pathway. See, e.g., Ihle, et al. (1997) Stem Cells 15(suppl. 1):105-111; Silvennoinen, et al. (1997) APMIS 105:497-509; Levy (1997) Cytokine Growth Factor Review 8:81-90; Winston and Hunter (1996) Current Biol. 6:668-671; Barrett (1996) Baillieres Clin. Gastroenterol. 10:1-15; and Briscoe, et al. (1996) Philos. Trans. R. Soc. Lond. B. Biol. Sci. 351:167-171. Of particular interest are the SH2 binding motifs described above.

Please replace the paragraph beginning on page 18, line 25, and continuing to page 19, line 7, with the following rewritten paragraph:

This invention contemplates use of isolated nucleic acid or fragments, e.g., which encode these or closely related proteins, or fragments thereof, e.g., to encode a corresponding polypeptide, preferably one which is biologically active. In addition, this invention covers isolated or recombinant DNAs which encode combinations of such proteins or polypeptides having characteristic sequences, e.g., of the DCRS5[[s]] SEQ ID NO:2) alone or in combination with others such as an IL-12Rβ1 (see Showe, et al. (1996) Ann. N.Y. Acad. Sci. 795:413-425; Gately, et al. (1998) Ann. Rev. Immunol. 16:495-521; GenBank U03187, NM_005535) subunit. Typically, the nucleic acid is capable of hybridizing, under appropriate conditions, with a nucleic acid sequence segment shown in ~~Table 1~~ SEQ ID NO:1, but preferably not with a corresponding segment of other receptors ~~described in Table 3~~ , SEQ ID NOs:3 or 4. Said biologically

active protein or polypeptide can be a full length protein, or fragment, and will typically have a segment of amino acid sequence highly homologous, e.g., exhibiting significant stretches of identity, to ~~one shown in Table 1~~ SEQ ID NO:2. Further, this invention covers the use of isolated or recombinant nucleic acid, or fragments thereof, which encode proteins having fragments which are equivalent to the DCRS5 proteins, e.g., intracellular portions. The isolated nucleic acids can have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others from the natural gene. Combinations, as described, are also provided, e.g., combining the DCRS5 with the IL-12β1, or their extracellular ligand binding portions as ligand antagonists. Diagnostic utilities are also clearly important, e.g., of polymorphic or other variants.

Please replace the paragraph beginning on page 19, line 20, and continuing to page 20, line 6, with the following rewritten paragraph:

A "recombinant" nucleic acid is typically defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence. Typically this intervention involves in vitro manipulation, although under certain circumstances it may involve more classical animal breeding techniques. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants as found in their natural state. Thus, e.g., products made by transforming cells with an unnaturally occurring vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such a process is often done to replace, e.g., a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a restriction enzyme sequence recognition site, or for some structure-function analysis. Alternatively, the process is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly available natural forms, e.g., encoding a fusion

protein. Restriction enzyme recognition sites are often the target of such artificial manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. This will include a dimeric repeat or fusion of the DCRS5 (SEQ ID NOs:1 or 2) with IL-12Rβ1 subunit. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode equivalent polypeptides to fragments of DCRS5 and fusions of sequences from various different related molecules, e.g., other cytokine family members.

Please replace the paragraph on page 20, lines 17-24, with the following rewritten paragraph:

A nucleic acid which codes for the DCRS5 (SEQ ID NO:2) will be particularly useful to identify genes, mRNA, and cDNA species which code for itself or closely related proteins, as well as DNAs which code for polymorphic, allelic, or other genetic variants, e.g., from different individuals or related species. Preferred probes for such screens are those regions of the receptor which are conserved between different polymorphic variants or which contain nucleotides which lack specificity, and will preferably be full length or nearly so. In other situations, polymorphic variant specific sequences will be more useful. Combinations of polymorphic variants of DCRS5 with variants of IL-12Rβ1 may also be diagnosed.

Please replace the paragraph beginning on page 20, line 35, and continuing to page 21, line 18, with the following rewritten paragraph:

Substantial identity in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 60% of the nucleotides, generally at least 66%, ordinarily at least 71%, often at least 76%, more often at least 80%, usually at least 84%, more usually at least 88%, typically at least 91%, more typically at least about 93%, preferably at least about 95%,

more preferably at least about 96 to 98% or more, and in particular embodiments, as high at about 99% or more of the nucleotides, including, e.g., segments encoding structural domains or other segments described. Alternatively, substantial identity will exist when the segments will hybridize under selective hybridization conditions, to a strand or its complement, typically using a sequence derived from ~~Table 1~~ SEQ ID NO:1. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, more typically at least about 65%, preferably at least about 75%, and more preferably at least about 90%. See, Kanehisa (1984) Nucl. Acids Res. 12:203-213, which is incorporated herein by reference. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, generally at least about 20 nucleotides, ordinarily at least about 24 nucleotides, usually at least about 28 nucleotides, typically at least about 32 nucleotides, more typically at least about 40 nucleotides, preferably at least about 50 nucleotides, and more preferably at least about 75 to 100 or more nucleotides. This includes, e.g., 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, etc., and other lengths.

Please replace the paragraph on page 22, lines 7-17, with the following rewritten paragraph:

Although site specific mutation sites are predetermined, mutants need not be site specific. Mammalian DCRS5 (SEQ ID NOs:1 or 2) mutagenesis can be achieved by making amino acid insertions or deletions in the gene, coupled with expression. Substitutions, deletions, insertions, or many combinations may be generated to arrive at a final construct. Insertions include amino- or carboxy terminal fusions. Random mutagenesis can be conducted at a target codon and the expressed mammalian DCRS5 mutants can then be screened for the desired activity, providing some aspect of a structure-activity relationship. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis. See also Sambrook, et al. (1989) and Ausubel, et al.

(1987 and periodic Supplements). Particularly useful constructs will be extracellular portions of the DCRS5 (SEQ ID NOs:1 or 2) associated with IL-12Rβ1 segments.

Please replace the paragraph on page 23, lines 27-32, with the following rewritten paragraph:

Candidate fusion partners and sequences can be selected from various sequence data bases, e.g., GenBank, c/o IntelliGenetics, Mountain View, CA; and BCG, University of Wisconsin Biotechnology Computing Group, Madison, WI, which are each incorporated herein by reference. In particular, combinations of polypeptide sequences provided in ~~Tables 1 and 3~~ Table 1 and SEQ ID NO:2 are particularly preferred. Variant forms of the proteins may be substituted in the described combinations.

Please replace the paragraph beginning on page 23, line 33, and continuing to page 24, line 3, with the following rewritten paragraph:

The present invention particularly provides muteins which bind cytokine-like ligands, and/or which are affected in signal transduction. Structural alignment of human DCRS5 with other members of the cytokine receptor family show conserved features/residues. See ~~Table 3~~ Table 1. Alignment of the human DCRS5 (SEQ ID NO:2) sequence with other members of the cytokine receptor family indicates various structural and functionally shared features. See also, Bazan, et al. (1996) Nature 379:591; Lodi, et al. (1994) Science 263:1762-1766; Sayle and Milner-White (1995) TIBS 20:374-376; and Gronenberg, et al. (1991) Protein Engineering 4:263-269.

Please replace the paragraph beginning on page 25, line 31, and continuing to page 26, line 7, with the following rewritten paragraph:

This invention also contemplates the use of derivatives of a DCRS5 (SEQ ID NO:2) other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives generally fall into three classes: (1) salts, (2) side chain and terminal residue covalent modifications, and (3) adsorption complexes, e.g., with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of a receptor or other binding molecule, e.g., an antibody. For example, a cytokine ligand can be immobilized by covalent bonding to a solid support such as cyanogen bromide activated Sepharose, by methods which are well known in the art, or adsorbed onto polyolefin surfaces, with or without glutaraldehyde cross linking, for use in the assay or purification of a cytokine receptor, antibodies, or other similar molecules. The ligand can also be labeled with a detectable group, e.g., radioiodinated by the chloramine T procedure, covalently bound to rare earth chelates, or conjugated to another fluorescent moiety for use in diagnostic assays.

Please replace the paragraph on page 27, lines 11-16, with the following rewritten paragraph:

DNA which encodes the protein or fragments thereof can be obtained by chemical synthesis, screening cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples. Natural sequences can be isolated using standard methods and the sequences provided herein, e.g., ~~in Table 1~~ SEQ ID NO:1 or 2. Other species counterparts can be identified by hybridization techniques, or by various PCR techniques, combined with or by searching in sequence databases, e.g., GenBank.

Please replace the paragraph on page 30, lines 32-35, with the following rewritten paragraph:

The source of DCRS5 (SEQ ID NOs:1 or 2) can be a eukaryotic or prokaryotic host expressing recombinant DCRS5, such as is described above. The source can also be a cell line, but other mammalian cell lines are also contemplated by this invention, with the preferred cell line being from the human species.

Please replace the paragraph on page 31, lines 13-18, with the following rewritten paragraph:

The DCRS5 (SEQ ID NO:2) proteins, fragments, or derivatives are suitably prepared in accordance with the above processes as typically employed in peptide synthesis, generally either by a so called stepwise process which comprises condensing an amino acid to the terminal amino acid, one by one in sequence, or by coupling peptide fragments to the terminal amino acid. Amino groups that are not being used in the coupling reaction typically must be protected to prevent coupling at an incorrect location.

Please replace the paragraph on page 32, lines 12-19, with the following rewritten paragraph:

Antibodies can be raised to the various mammalian, e.g., primate DCRS5 (SEQ ID NO:2) proteins and fragments thereof, both in naturally occurring native forms and in their recombinant forms, the difference being that antibodies to the active receptor are more likely to recognize epitopes which are only present in the native conformations. Antibodies recognizing epitopes presented by the combination, e.g., functionally, of the DCRS5 with the IL-12Rβ1 are also contemplated. Denatured antigen detection can also be useful in, e.g., Western analysis. Anti-idiotypic antibodies are also contemplated, which would be useful as agonists or antagonists of a natural receptor or an antibody.

Please replace the paragraph beginning on page 34, line 31, and continuing to page 35, line 2, with the following rewritten paragraph:

A cytokine receptor protein that specifically binds to or that is specifically immunoreactive with an antibody generated against a defined immunogen, such as an immunogen consisting of the amino acid sequence of SEQ ID NO: 2, is typically determined in an immunoassay. The immunoassay typically uses a polyclonal antiserum which was raised, e.g., to a protein of SEQ ID NO: 2. This antiserum is selected to have low crossreactivity against other cytokine receptor family members, e.g., IL-12Rβ receptor subunit (SEQ ID NO:4) or IL-6 receptor subunit gp 130 (SEQ ID NO:3), preferably from the same species, and any such crossreactivity is removed by immunoprecipitation prior to use in the immunoassay.

Please replace the paragraph on page 36, lines 32-35, with the following rewritten paragraph:

Purified DCRS5 (SEQ ID NO:2) can be coated directly onto plates for use in the aforementioned ligand screening techniques. However, non neutralizing antibodies to these proteins can be used as capture antibodies to immobilize the respective receptor on the solid phase, useful, e.g., in diagnostic uses.

Please replace the paragraph on page 42, lines 28-32, with the following rewritten paragraph:

Drug screening using DCRS5 (SEQ ID NO:2) or fragments thereof can be performed to identify compounds having binding affinity to the receptor subunit, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity and is therefore a blocker or antagonist in that it blocks the activity of the ligand.

Please replace the paragraph on page 45, lines 16-20, with the following rewritten paragraph:

PCR primers derived from the DCRS5 sequence are used to probe a human cDNA library. Sequences may be derived, e.g., from ~~Table 1~~ SEQ ID NO:1, preferably those adjacent the ends of sequences. Full length cDNAs for primate, rodent, or other species DCRS5 are cloned, e.g., by DNA hybridization screening of λgt10 phage. PCR reactions are conducted using T. aquaticus Taqplus® DNA polymerase (Stratagene) under appropriate conditions.

Please replace the paragraph on page 46, lines 13-15, with the following rewritten paragraph:

Alternatively, two appropriate primers are selected from ~~Table 1~~ SEQ ID NO:1. RT-PCR is used on an appropriate mRNA sample selected for the presence of message to produce a cDNA, e.g., a sample which expresses the gene.

Please replace the paragraph on page 49, line 11, with the following rewritten paragraph:

VI. Production of mammalian DCRS5 (SEQ ID NO:2) protein

Please replace the paragraph on page 50, line 23, with the following rewritten paragraph:

VIII. Production of fusion proteins with DCRS5 (SEQ ID NOs:1 or 2)